REMARKS

The Invention

The present claims are directed to methods and compositions that make use of the antibiotic, rifalazil, for treating a subject having an infection of *Clostridium (C.) difficile.*

The Office Action

Claims 1-75 are pending. Claims 1-75 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 54-75 are rejected under 35 U.S.C. § 101 for being directed to non-statutory subject matter. Claims 1-11, 13-18, 20-27, 29-45, 48-50, 54-65, and 67-73 are rejected under 35 U.S.C. § 102(e) for anticipation by Michaelis et al. (U.S. Patent Application Publication Number 2004/0034021; hereafter "Michaelis"). Claims 1-11 and 54-58 are rejected under 35 U.S.C. § 103(a) for obviousness over Chamberland et al. (U.S. Patent No. 6,114,310; hereafter "Chamberland") in combination with Rose et al. (U.S. Patent No. 6,316,433; hereafter "Rose"). Claims 13, 34, 35, 37-53, 59, and 73-75 are rejected under 35 U.S.C. § 103(a) for obviousness over Chamberland in combination with Rose and further in combination with Bostwick et al. (U.S. Patent No. 5,773,000; hereafter "Bostwick"). Claims 12, 14-33, 36, and 60-72 are rejected under 35 U.S.C. § 103(a) for obviousness over Chamberland in combination with Rose and further in view of statements made in Applicant's specification. Each of these rejections is addressed in detail below.

Support for New Claims

New claim 76 has been added to include the limitation that the rifalazil is administered orally. Support for this claim can be found throughout the specification and the claims, for example, in claim 11. No new matter has been added by this amendment.

Rejection of Claims 1-75 under 35 U.S.C. § 112

Claims 1-75 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In particular, the Office has rejected the claims on the grounds that the specification, while enabling for treating a subject having an infection of *C. difficile* or inhibiting infection of *C. difficile* in a subject, does not reasonably provide enablement for preventing infection of C. *difficile* in a subject. Applicant respectfully disagrees.

Claims 1-75 are directed to methods and compositions that make use of the antibiotic, rifalazil, for treating a subject having an infection of *C. difficile* or preventing an infection of *C. difficile* in a subject. Applicant submits that the specification provides enablement for both the treatment and the preventive methods.

In particular, dosages and methods of administration are described in detail throughout the specification, for example, at page 7, lines 13-24:

> The dosage of rifalazil can range from about 0.01 to 1000 mg. The dosage of rifalazil is normally about 1 to 1000 mg (desirably about 1 to 100 mg, more desirably about 1 to 50 mg, and even more desirably about 1 to 25 mg). The rifalazil may be given daily (e.g., once, twice, three times, or four times daily) or less frequently (e.g., once every other day, once or twice weekly, or monthly). (Page 7, lines 13-17.)

In addition, an "effective amount" is defined at page 5, line 19 to page 6, line 10 in terms of *eradication and prevention* of a *C. difficile* infection as well as a reduction in the symptoms of *C. difficile*-associated disease. A portion of this citation is reproduced below.

> By "an effective amount" is meant the amount of rifalazil or rifalazil in combination with one or more additional antibiotics required to result in the *C. difficile* being eradicated from the subject, or to prevent an infection of *C. difficile*, as determined by a diagnostic test that detects *C. difficile*. One example of a diagnostic test is the use of a commercially available enzyme-linked immunoassay (ELISA; Immunocard; Meridian Diagnostics, Inc., Cincinnati, Ohio) to detect the presence of *C. difficile* toxin A protein in cecal content extracts. Another example of a diagnostic test is the use of a cytotoxicity assay using human fibroblast cells (Toxi-Titer; Bartels, Inc., Issaquah, WA) to detect the presence of *C. difficile* toxin B. Both of these examples can be found in McVay and Rolfe (Antimicrobial Agents and Chemo. 44:2254-2258, 2000). (Page 5, lines 19-29.)

The diagnostic tests described can be used to determine the effective amount required to prevent a *C. difficile* infection by detecting any presence of the microorganism in the subject.

Furthermore, in Example 1, animal studies are described that demonstrate the efficacy of rifalazil for both the treatment and prevention of a *C. difficile* infection. For

example, as stated on page 15, lines 9-11, of Example 1:

> [A]antibiotic treatment is then administered orally, intravenously, or intraperitoneally, either simultaneously or 24 hours after *C. difficile* administration.

Simultaneous administration of rifalazil with *C. difficile* administration is used as a prophylactic protocol (i.e., to prevent *C. difficile* infection) while the administration of rifalazil 24 hours after *C. difficile* administration is used as a therapeutic protocol (i.e., after *C. difficile* infection has occurred). These teachings in the specification evidence the fact that Applicant has taught that rifalazil may be administered for preventing *C. difficile* infection.

Moreover, the methods and guidelines described in the specification and, in particular, in Example 1 have been demonstrated by Anton et al. ("Rifalazil Treats and Prevents Relapse of *Clostridium difficile*-Associated Diarrhea in Hamsters," *Antimicrobial Agents and Chemotherapy* 48:3975-3979 (2004) (Exhibit A) [1]) to be effective for preventing *C. difficile* infection and *C. difficile*-associated diarrhea after infection. Anton et al. describes experimental results demonstrating the efficacy of rifalazil in preventing or treating clindamycin-induced cecitis in a Golden Syrian hamster model of *C. difficile*-associated disease. The dosages and routes of administration of rifalazil are carried out exactly as described in the specification and the animal model used is the same animal model described in Example 1 of the specification.

[1] Applicant notes that the inventor of the present application is an author on this paper.

Anton et al. shows the survival analysis of hamsters infected with *C. difficile* and treated at day 0 (prophylactic treatment, Figure 2) or 24 hours after infection (therapeutic protocol, Figure 3) with vancomycin or rifalazil. The results clearly show that none of the animals treated with rifalazil in the prophylactic protocol or therapeutic protocol showed any sign of disease during treatment. In fact, 100% of the rifalazil-treated animals survived. Furthermore, the rifalazil-treated animals showed no sign of disease up to 34 days post *C. difficile* infection and no sign of *C. difficile* toxins. These results indicate that rifalazil not only prevents disease from occurring during treatment but can also prevent the reappearance of *C. difficile*-associated disease associated with relapsing infection after treatment is discontinued. The authors conclude from these results that, "rifalazil prevents and treats clindamycin-induced, *C. difficile*-associated infection in Syrian hamsters in vivo." (Page 3978). Applicant submits that the data shown in Exhibit A clearly demonstrates that, using the same animal model and the same therapeutic regimens described in the specification, rifalazil was highly effective in both treating and preventing *C. difficile* infection as recited in claims 1-75.

In sum, as the specification enables the scope of the claims, the rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

Rejection of Claims 54-75 under 35 U.S.C. § 101

Claims 54-75 are rejected for being directed to non-statutory subject matter. Citing M.P.E.P. § 706.03(a)IA, the Office states that claim 54 recites "instruction" as part of the claimed product/composition and a mere arrangement of printed matter is not within the statutory classes. Applicants respectfully disagree with this characterization of the claims as "a mere arrangement of printed matter."

Claim 54 is directed to a pharmaceutical pack comprising rifalazil in an amount effective to treat a subject having an infection of *C. difficile* or prevent an infection of *C. difficile* and instructions for administering the rifalazil to the subject. Claims 55-75 depend from claim 54.

As an initial matter, Applicant points out that the Office has mischaracterized claims 54-75 as "a mere arrangement of printed matter." Claims 54-75, rather than being directed to printed matter or a mere arrangement of printed matter per se, cover a pharmaceutical pack that includes rifalazil and instructions for administering the rifalazil to the subject.

Furthermore, printed matter, when included as part of a combination, does have patentable weight as demonstrated by the CCPA decision to overturn the Examiner in *In re Miller* 418 F.2d 1392, 164 U.S.P.Q. 46 (CCPA 1969), cited in M.P.E.P. § 706.03(a)IA and by the Office in the present rejection. In *Miller*, the claims on appeal were directed to a measuring receptacle having quantity measuring indicia and a legend on the

receptacle or attached to it. The Examiner allowed claims 9 and 14, which included the legend, but rejected claims 10-13, in which he characterized the indicia and the legend as "unpatentable printed matter." In reviewing this characterization, the CCPA stated:

> We note that the examiner himself recognizes the fact that printed matter, in an article of manufacture claim, can be given "patentable weight." He did so in allowing claims. His characterization of printed matter as "unpatentable" is beside the point; no attempt is here being made to patent printed matter as such. The fact that printed matter by itself is not patentable subject matter, because non-statutory, is no reason for ignoring it [the printed matter] when the claim is directed to a combination.

Applying this holding to claims 54-75, the inclusion of instructions as part of a combination (i.e., the pharmaceutical pack), should not be construed as an attempt to patent printed matter as such. This rejection should be withdrawn.

Rejection of Claims 1-11, 13-18, 20-27, 29-45, 48-50, 54-65, and 67-73 under 35 U.S.C. § 102(e)

Claims 1-11, 13-18, 20-27, 29-45, 48-50, 54-65, and 67-73 stand rejected under 35 U.S.C. § 102(e) for anticipation by Michaelis. Applicant respectfully submits that this rejection has been applied in error.

Michaelis was filed on June 3, 2003 and claims priority to U.S. Provisional Application Nos. 60/385,532, filed June 3, 2002 ("provisional I"); 60/406,873, filed August 29, 2002 ("provisional II"); 60/412,958, filed Sept. 23, 2002 ("provisional III"); and 60/444,570, filed Feb. 3, 2003 ("provisional IV"). The present application claims

priority to U.S. Provisional Application Nos. 60/406,873, filed Aug. 29, 2002 (provisional II) and 60/444, 570, filed Feb. 3, 2003 (provisional IV).

In view of the above priority dates, for the present anticipation rejection to stand, the claimed subject matter would need to be disclosed in Michaelis' patent application 60/385,532 (provisional I), the only priority document that antedates the priority date of the present claims. A review of this priority document, a copy of which is provided as Exhibit B, reveals that there is no mention of *C. difficile* or the treatment of *C. difficile*. Accordingly, Michaelis cannot anticipate any of claims 1-11, 13-18, 20-27, 29-45, 48-50, 54-65, or 67-73, and this rejection should be withdrawn.

Rejection of Claims 1-11 and 54-58 under 35 U.S.C. § 103(a)

Claims 1-11 and 54-58 remain rejected for obviousness over Chamberland in view of Rose. Applicant respectfully traverses this rejection.

Applicant's claims are directed to methods of treating *C. difficile* – an organism considered to be difficult to eradicate – with the antibiotic, rifalazil. This invention is reflected in independent claim 1 and dependent claims 2-11, which cover these methods, as well as independent claim 54 and dependent claims 55-58, which feature compositions that include rifalazil in an amount effective to treat a *C. difficile* infection and instructions for administering the rifalazil to the subject.

In maintaining this rejection, the Office states that although Chamberland's focus

may not specifically be rifamycin, Chamberland does list rifamycin for use with the efflux pump inhibitors for the treatment of microbial infections and that the combination of this teaching with Rose's teaching that rifalazil is a known rifamycin renders the present invention obvious. Applicant respectfully disagrees.

Chamberland describes compounds referred to as efflux pump inhibitors and their use for preventing the export of substrate molecules from cells. Chamberland generally discusses treatment of microbial infections by methods that always include the combined use of efflux pump inhibitors and antimicrobial agents.

Chamberland does not teach the use of a rifamycin or any antimicrobial agent alone for the treatment of any microbial infection. In fact, as acknowledged by the Office, Chamberland's methods and compositions all require the combination of an antimicrobial agent with an efflux pump inhibitor.

In addition, there is no particular focus in Chamberland on rifamycins. Rifamycins are not called out specifically for the treatment of *C. difficile* or any other specific microbial infection. In fact, it is efflux pump inhibitors, and not antibiotics, that Chamberland touts as effective antibacterial compounds. Moreover, rifamycins at best are listed as just *one of nine different classes of possible antibacterial agents* and *one of 141 possible antibacterial agents* that Chamberland indicates can be used *in combination* with an efflux pump inhibitor. In the absence of any specific suggestion or guidance, the selection of rifamycins from the long list of antibacterial agents is nothing more than

a 1 in 141 chance occurrence.

Furthermore, nowhere does Chamberland state that rifamycins can or should be used to treat *C. difficile*, as asserted by the Office. *C. difficile* is only mentioned as one of *89 different bacteria* "to be inhibited through the use of an efflux pump inhibitor." *C. difficile* is nowhere else mentioned in the specification nor is it called out specifically for treatment by a rifamycin or any other particular antibiotic. In the absence of any specific suggestion or guidance, the selection of *C. difficile* from Chamberland's long list of bacteria is nothing more than a 1 in 89 chance occurrence.

In addition, as unlikely as the selection of either *C. difficile* or a rifamycin is alone based on Chamberland's teachings, the selection of the combination of the two is even less likely. *Indeed, the probability that a skilled artisan, reading Chamberland, would arrive at the combination of rifamycins and C. difficile is 1 in 12,549.* In the absence of any suggestion or guidance towards the selection of either of these, let alone the combination, the skilled artisan reading Chamberland would not be led to the selection of a rifamycin to treat *C. difficile* and the Office's characterization of Chamberland as anything more than allowing for this 1 in 10^4 possibility reads more into the Chamberland teaching than is disclosed.

Applicant also points out that the selection of antimicrobial agents for the treatment of *C. difficile*, in particular, is further complicated by the fact that, unlike many bacterial infections, *C. difficile* is actually caused by treatment with antibiotics typically

used to treat other bacterial infections.

As attested to in the accompanying Declaration of Dr. Charalabos Pothoulakis, a known expert in the field of microbial infections and gastrointestinal disease, *C. difficile* is a particularly difficult microorganism to treat because antibiotics, typically used to treat bacterial infections, can actually contribute to *C. difficile*-associated disease by altering the environment in the colon and allowing *C. difficile* to flourish. Even if the antibiotic used for therapy is effective initially, there is a high incidence (15 to 20%) of relapsing diarrhea following an initial response, and this relapsing *C. difficile* infection is one of the most difficult infections to treat because, in this case, the antibiotic therapy has the potential to disrupt the normal environment of the colon and further encourage the growth of the *C. difficile* organism.

Dr. Pothoulakis attests to the fact that most, if not all, antibiotics, including the vast majority of those listed by Chamberland, can alter the environment in the colon in a way that allows *C. difficile*, if present in the environment, to flourish.

As a result, even if one were to accept, for argument's sake, that generally the selection of antibacterial agents for the treatment of a bacterial infection is as simple as picking one agent and one bacteria from Chamberland's lists, in the case of *C. difficile*, the majority of choices presented would actually cause or encourage the *C. difficile* infection - not treat or prevent it.

In sum, Applicant submits that the selection of rifamycins for the treatment of *C.*

difficile based on the teachings of Chamberland is nothing more than a 1 in 10^4 chance occurrence. This choice is further complicated by the fact that *C. difficile* is at best not treated effectively and at worst caused by the vast majority of antimicrobial agents listed in Chamberland. Reliance on Chamberland should be withdrawn.

Turning to the secondary reference, Rose, this reference describes a method for the treatment of a bacterial infection using a once-weekly or twice-weekly administration of rifalazil. Even if Applicant stipulates that Rose "teaches that rifalazil is a known rifamycin that is known to treat bacterial infections," as suggested by the Office, this does not remedy the deficiencies of Chamberland. As indicated above, Chamberland does not teach that rifamycins should be used to treat infections of *C. difficile* as required by the claims. Accordingly, these references even in combination do not support a *prima facie* case of obviousness. The § 103 rejection of claims 1-11 and 54-58 should be withdrawn.

Rejection of Claims 13, 34, 35, 37-53, 59, 73-75 under 35 U.S.C. § 103(a)

Claims 13, 34, 35, 37-53, 59, and 73-75 remain rejected for obviousness over Chamberland in view of Rose and in further combination with Bostwick. Applicant respectfully traverses this rejection.

Claims 13, 34, 35, 37-53, 59 and 73-75 feature methods and compositions for treating a subject having a *C. difficile* infection by administering to the subject an

effective amount of rifalazil in combination with one or more particular antibiotics.

For this rejection, the Office states that the teachings of Chamberland and Rose, as described for the previous § 103 rejection, render the present claims obvious when further combined with Bostwick's teaching that vancomycin and metronidazole are known to treat *C. difficile* in combination with other active agents. This rejection is traversed because Bostwick does not cure the deficiencies of Chamberland described above.

Specifically, Bostwick teaches the use of an antibody having activity against *C. difficile* and its use for treating a human suffering from a *C. difficile* infection. Bostwick states that the use of an antibody therapeutic is particularly effective in the treatment of *C. difficile* because it does not disrupt the colonic flora, one of the limitations of antibiotic therapies. Bostwick also describes the combination of their antibody therapy with the known antibiotics vancomycin, bacitracin, and metronidazole.

Applicant agrees that vancomycin and metronidazole were known to ameliorate *C. difficile* infections at the time the invention was made. However, these treatments were also known to be ineffective in up to 20% of cases, thereby presenting a need for improved methods for treating *C. difficile* infections. Bostwick's improvement features the use of an antibody (a non-antibacterial agent) having specific activity against *C. difficile*. Applicant's improvement features the use of rifalazil, an antibiotic *that was not previously known* to be effective for the treatment of *C. difficile* infections.

As discussed in detail above, the primary reference, Chamberland, does not teach that rifamycins can be used to treat *C. difficile* infections. Arrival at the combination of rifamycins and *C. difficile* from Chamberland is a 1 in 10^4 possibility and one which is further complicated by the fact that other combinations of antibacterial agents disclosed in Chamberland would either cause or enhance a *C. difficile* infection. Rose does not remedy this deficiency. Bostwick also does not remedy this deficiency because Bostwick makes no mention of rifamycins or rifalazil for the treatment of a *C. difficile* infection. In fact, as cited by the Office in the present action Bostwick suggests that "it is also advantageous to administer to patients suffering from *C. difficile* associated diseases a combination of the antibodies of the present invention *with antibiotics prior known* for treating pseudomembranous colitis and/or antibiotic associated diarrhea." Applicant reiterates that the use of rifalazil for the treatment of *C. difficile infections or C. difficile associated diarrhea was not prior known*. Therefore, Bostwick's combination of antibodies with antibiotics prior known for treating *C. difficile*-associated disease does not apply to the present invention. The combination of Chamberland, Rose, and Bostwick therefore does not support a *prima facie* case of obviousness for any of claims 13, 34, 35, 37-53, 59, or 73-75. This rejection should also be withdrawn.

Rejection of Claims 12, 14-33, 36, and 60-72 under 35 U.S.C. § 103(a)

Claims 12, 14-33, 36, and 60-72 stand further rejected for obviousness over Chamberland in view of Rose and in further combination with the admission of Applicant in his specification. Applicant respectfully traverses this rejection.

In maintaining this rejection, the Office combines the arguments relied on for the previous obviousness rejections with the additional assertion that, although Chamberland does not list all of the recited antibiotics as being known, Applicant admits in his own specification that the recited drugs are known and have known dosages.

The invention covered by claims 12, 14-33, 36, and 60-72 features the use of an effective amount of rifalazil in combination with one or more additional agents, including second antibiotics, for treating a subject having an infection of *C. difficile*. The presence of a statement in Applicant's specification that the additional drugs that are to be used in combination with rifalazil in the methods and compositions of the present invention are known and have known dosages does not render the present invention obvious. It is the combination of such known drugs with *rifalazil* that is claimed in claims 12, 14-33, 36, and 60-72. Applicant maintains that this combination was not known at the time the invention was made because rifalazil was not taught or suggested by Chamberland or Rose (or elsewhere in the prior art) for use in treating *C. difficile*.

As presented above, Chamberland's inclusion of rifamycins as one of nine classes of antibacterial agents and one of 141 possible antibacterial agents and *C. difficile* as one

of 89 possible microbial infections does not amount to a disclosure of rifamycins for the treatment of a *C. difficile* infection. At best it amounts to a 1 in 10^4 possibility (among other possibilities that would encourage *C. difficile* growth) and should not be used as the basis for this obviousness rejection. The fact that other antibiotics were known and their dosages determined is of no significance to the patentability of Applicant's basic invention – the use of rifalazil to treat *C. difficile*. The § 103 rejection of claims 12, 14-33, 36, and 60-72 should be withdrawn.

CONCLUSION

Applicant submits that the claims are now in condition for allowance and such action is respectfully requested.

Enclosed is a check for $25 in payment of the excess claims fee. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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